REMARKS

This is intended as a full and complete response to the Office Action dated July March 5, 2009, having a shortened statutory period for response set to expire on June 5, 2009.

Claims 1-12 and 17-29 remain pending in the application and are shown above. Claims 1-12 and 17-29 stand rejected by the Examiner. Please consider the claims pending in the application for the reasons discussed below.

Claim Rejections under 35 U.S.C. § 103

Claims 1-3, 5-11, 17-20, 22-24, 27 and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Parikh et al.* (US 2002/0106403, hereinafter "*Parikh*") in view of *Caruso et al.* (EP 1116516, hereinafter "*Caruso*"). Applicants respectfully traverse the rejection.

To establish prima facie obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. (*See* MPEP 2143.03).

Parikh teaches dispersing surface stabilized microparticles (drug particles) throughout a bulking matrix which dissolves in a rapid disintegration time upon contact with an aqueous environment, thereby rapidly releasing the stabilized microparticles without having particle agglomeration phenomenon.

Parikh does not teach or suggest capsules having a core and a shell structure. Particularly, *Parikh* does not teach, suggest, or otherwise render obvious "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, the shell comprising a high permeability to release the slightly soluble active ingredient within 60 minutes," as recited in claim 1.

Parikh discloses a rapidly dispersing solid dosage consisting of particles, dispersed throughout a bulking matrix optionally including a releasing agent, buffering salts and pH adjusting agents. (*See Parikh*, page 5, claim 1, paragraphs [0030] and

[0033]). The particles consist of water insoluble or poorly soluble compounds and can be prepared according to the methods disclosed in US 5,091,187 and US 5,091,188 (*Id.* page 2, paragraph [0010]).

Parikh's surface stabilizing agent, of which at least one is a phospholipid (*Parikh*, page 2, paragraph [0014]), *i.e.,* the phospholipid coating of *Parikh*'s particles, is quite different from the shell structure of the particles of the present application, which comprises essentially a material with **high permeability for the slightly soluble active ingredient** and comprises a **complex of at least one polyelectrolyte and a counter ion** to the polyelectrolyte. (*See* present claim 1).

The deposited layer-by-layer (LbL) polyelectrolyte shell of the present application is also highly permeable for water because of the ionic nature of the polyelectrolytes, therefore the shell recited in present claim 1 is highly permeable both for the drug and for the solvent. Functionally, the shell of the particle represents a polyelectrolyte cage. Both properties combined allow very fast drug release by dissolution even for very slightly soluble core substances.

The Examiner alleges in the Office Action on page 3 that *Parikh*'s microparticles include a shell and that this shell implicitly allows diffusion. The Examiner also alleges that *Parikh* teaches the rate of dissolution and release can be intermediate (75% disintegration in 15 minutes), thereby implying that the shell of the microparticle allows the diffusion and release of the active ingredient such that 75% of the microparticle disintegrate in 15 minutes, *i.e.,* a stable aqueous suspension during release of the active ingredient is implicit. Applicants respectfully disagree.

As discussed in Applicants' previous response, *Parikh*'s surface modifier is **adsorbed** on to the surface of micronized particles and dissolved together with the microparticles, which implies a non-stable capsule shell. (*See Parikh*, paragraph [0010]). The term "dissolve" or "disintegrate" as described in *Parikh*'s specification clearly suggests a non-stable capsule shell. According to *Merriam Webster Online Dictionary*, the term "disintegrate" is defined as (1) to break or decompose into constituent elements, parts, or small particles, (2) to destroy the unity or integrity of an

object. Also, the term "dissolve" is defined as to become dissipated or decomposed, or to become fluid. (*See* http://www.merriam-webster.com/dictionary/disintegrate; http://www.merriam-webster.com/dictionary/dissolve, accessed June 10, 2009). The explanations for the term "dissolve" or "disintegrate" therefore matches *Parikh*'s description that the surface modifier is dissolved together with the microparticles.

The inference that the adsorbed surface modifier is dissolved during dissolution of the microparticles is further supported by *Parikh*'s own argument made during the prosecution history of that particular application with USPTO. In response to a prior art rejection, *Parikh* describes "*the soluble drug is first mixed with surface stabilizing agents to form an aqueous suspension that is subjected to particle fragmentation to form a homogeneous aqueous suspension. Thereafter, the homogeneous suspension is admixed with a matrix prior to drying to form drug-containing particles that rapidly dissolve and release the drug component in an aqueous environment.*" (*See* US 2002-0106403, Applicant Arguments/Remarks, 2004-12-16, page 20, paragraph 1) Therefore, it is evident that the adsorbed surface modifier, *i.e.,* the alleged shell, is not in a stable status that allows the drug component to diffuse through during release of the drug component, but rather rapidly **dissolved** together with the drug component in an aqueous environment as described in *Parikh*'s disclosure.

As none of the descriptions shows or implies diffusion or something sustained in a certain form in order for an object to penetrate, pierce or diffuse through as alleged by the Examiner *("[t]here is penetration as the shell dissolves"*, see Advisory Action dated October 17, 2008, page 2), Applicants respectfully request the Examiner reconsider the pending claims in view of differences discussed herein.

Even when considering *Parikh*'s phospholipid coating (*i.e.,* surface modifiers) as a shell, this shell does not allow fast release of the drug. In fact, *Parikh*'s microparticles disintegrate by removal of the phospholipid coating. Specifically, *Parikh*'s coating fulfills the role of an agglomeration preventing barrier, being hydrophobic at one side and hydrophilic on the other. (*See* col. 8, lines 4-8, "*Unique to my invention is the use of phospholipids to shield the hydrophobic surface of the crystalline drug and to provide*

additional membranous barriers against reassociation of the crystals"). Functionally, it allows enveloping of hydrophobic (slightly soluble) core sub-particles, generated during their homogenizatioin and prevents their agglomeration, once the preparation is exposed to solvent. The phospholipid coating fulfills the barrier function also when the surrounding matrix disperses (disintegrates). However, as any other lipid membrane, it restricts water transport considerably, allowing water diffusion only against solute concentration gradients (osmosis). If, however, the lipid encapsulated during is only slightly water soluble, osmosis will hardly be initiated and thus no water diffusion occurs.

In addition to a restricted water diffusion through the phospholipid coating, a slightly water soluble drug, *i.e.,* a hydrophobic drug, hardly diffuses through a phospholipid coating is generally known to a skilled person. Any diffusion through the phospholipid coating is significantly restricted so that no release through penetration of the phospholipid coating occurs.

The restricted diffusion of the drug through the phospholipid coating corresponds to the emphasized object of *Parikh* to provide a rapidly dispersing solid dosage form for slightly soluble compounds. (*See Parikh*, page 1, paragraph [0003]). Accordingly, the released entities of *Parikh*'s dosage form are primary particles, stabilized with surface modifiers (*Id.* page 2, paragraph [0013]). The dissolution characteristic of their cores was never in the focus of *Parikh* nor is it disclosed. Table 1 on page 4 of *Parikh* lists experimental data for different formulations with measured particle sizes from 1-85 µm and a **disintegration time**, not dissolution time.

Any drug moiety, once freely accessible to the solvent is prone to aggregate in contact with a similar freely accessible drug moiety. *Parikh*'s phospholipid coating barrier prevents this reaggregation and *nolens volens* represents a barrier for the solute as well. The drug in *Parikh*'s particles can therefore be released only by disintegration of the particle, not by diffusion, since the phospholipid coating represents a stable barrier. The resulting drug release rate therefore will depend on the composition of the particles as a whole (*Id.* page 4, paragraph [0025]), which means that the administration

mechanism for drugs prepared according to *Parikh* is defined by the disintegration of the phospholipid coating.

With respect to combining the teachings of *Parikh* and *Caruso* as proposed by the Examiner, Applicants submit that any such combination is erroneous since *Caruso* uses a completely different approach than *Parikh.*

A polyelectrolyte cover is used by *Caruso* for obtaining a **constant release rate over a long time period**. (*See* paragraph [0012] on page 3, lines 19-20). Paragraph [0032] on page 5 of *Caruso* also refers to a **controlled** release of the encapsulated material with a **high** diffusion barrier for obtaining a sustained release of the encapsulated material. (*See* paragraph [0012], lines 29-34). A skilled person would be therefore, when considering *Caruso*, directed to sustained release systems and would not be motivated to combine with *Parikh*, which teaches a rapidly dispersing solid dosage, to form fast-releasing capsules having a **high** permeability for a slightly soluble active ingredient.

In addition, although *Caruso* discloses that the permeability and porosity of the capsule can be controlled by the selection of the polyelectrolyte used for the capsule shell and the number of polyelectrolyte layers used, thicker shells, reduced pore sizes and porosity of the shells, and smoother outer surface are characteristics suggested and desirable in terms of *Caruso*'s capsules. (*See* page 4, lines 5-9). Particularly, amphiphilic substance is suggested in *Caruso*'s capsules to control the porosity. In view of paragraph [0038] stating that the type of amphiphile determines the porosity and hence the permeability, it is evident that small molecular surfactants, for example, phospholipids as used by *Caruso*, form very small pores and hence reduce the permeability of the polyelectrolyte layer, so that it is possible to achieve a controlled release of the encapsulated material by releasing a small amount of active substance constantly over a long time period with a high diffusion barrier across the wall of the capsule, as described in *Caruso's* disclosure.

In view of *Parikh*'s statement that the key aspect of his invention is the phospholipid barrier, which additionally prevents any fast release, a skilled artisan would

not consider an additional polyelectrolyte coating of *Parikh*'s particles according to *Caruso* as such polyelectrolyte coating atop the phospholipid coating would stabilize it even further. A phospholipid coating stabilized by a polyelectrolyte coating hardly disintegrates, so that no drug release through disintegration occurs.

Due to the phospholipid coating, the diffusion of solvent and drug is also significantly restricted. Hence, a potential drug release would be remarkably slowed down from a medical point of view. The resulting inhibition of drug release would lead away from the declared goal of the subject application for fast release drug formulation and therefore, the approach to combine *Caruso* with *Parikh* would lead a skilled artisan away from the present invention.

Meanwhile, the use of polyelectrolytes would not fit into *Parikh*'s essential process of preceding particle fragmentation of the water insoluble compound. *Parikh* uses phospholipids as immediate surface modifiers during the disintegration process of the water insoluble compound into a homogeneous suspension of micron and submicron particles, *i.e.,* **during the whole homogenization procedure** for preparing the microparticles. (See *Parikh*, paragraph [0017]). An immediate polyelectrolyte multilayer coating of particles during their homogenization is impossible. In contrast to *Parikh*, *Caruso*'s micro- and nanoparticles are already dispersed, the Layer-by-Layer (LbL)-coating procedure has been developed accordingly. The essence of *Parikh*'s invention, *i.e.,* to have the encapsulating surfactant at the freshly broken particle surface during the microparticle formation process, does not allow its substitution, without loosing the key aspect of *Parikh*'s invention. Therefore, this hypothetical alternative would be disregarded by a skilled artisan.

Therefore, *Caruso* gives no hint whatsoever to combine the possible tuning of release properties of polyelectrolyte capsules with a fast disintegrating coherent matrix to provide a fast release solid dosage form. Applicants respectfully submit that a notional combination of *Parikh* and *Caruso* is an impermissible hindsight consideration and request withdrawal of the rejection to claim 1 and claims dependent thereon.

Similarly, claims 18 and 24 includes the similar limitation "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient." In view of the reasons stated above, claims 18 and 24 should be patentably distinct over *Parikh* and *Caruso*. Therefore, withdrawal of the rejection to claims 18 and 24 and claims dependent thereon is respectfully requested.

Claims 4, 25 and 28 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Parikh* and *Caruso* as applied above, and further in view of *Allen et al.* (US 6,187,337, hereinafter "*Allen*"). Applicants respectfully traverse the rejection.

Parikh and *Caruso* are discussed above. *Allen* is concerned with a rapidly dissolving dosage form which disintegrates or dissolves in a matter of just **a few seconds** once placed into an aqueous environment. (*See* Abstract).

Allen does not cure the deficiencies of *Parikh* and *Caruso* as discussed herein with respect to the independent claims from which claims 4, 25, and 28 depend. Although *Allen* mentions the ratio of mannitol and gelatin, *Allen* does not teach or suggest the active material to be encompassed by a material with high permeability. Specifically, *Allen* does not teach, suggest, or otherwise render obvious "fast-releasing capsules having a high permeability for the slightly soluble active ingredient," and "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, the shell comprising a high permeability to release the slightly soluble active ingredient within 60 minutes," as recited in claim 1. Since claim 4, 25 and 28 depends from claim 1 and contains all the limitations of claim 1, Applicants respectfully assert that claim 4, 25 and 28 should be allowable at least for the same reasons stated above. Withdrawal of the rejection to claim 4, 25 and 28 is respectfully requested.

Claims 12 and 21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Parikh* in view of *Caruso* and further in view of *Virgalitto et al* (US 2005/0089548). Applicants respectfully traverse the rejection.

Parikh and *Caruso* are discussed above. *Virgalitto* teaches a **sustained** release mechanism using microcapsules (edible film) contained with an active agent. *Virgalitto* discloses the film-forming material is capable of rapidly dissolving in water or oral cavity to release the active agent contained in the film. (*See* paragraph [0024]). *Virgalitto* also discloses preparing an aqueous solution of film-forming materials, adding microcapsules comprising active agent, casting the resultant mixture onto a releasable backing media, and drying the film. (*See* Paragraph [0074])

Virgalitto fails to overcome the deficiencies of *Parikh* and *Caruso* as discussed herein with respect to the independent claims from which claim 12 depends. Although *Virgalitto* mentions the use of microcapsules containing active agents, *Virgalitto*'s film is **rapidly dissolved**, break-down and distintegrated upon contact with moisture to release the active agent. (*See* paragraph [0019]) As Applicants discussed above with respect to claim 1, a film that is rapidly dissolved, break-down and disintegrated upon contact with moisture implies a non-stable shell that would not allow diffusion of the active ingredient while maintaining a stable during release of the active ingredient, as opposite to Applicants' claim 1. Since *Virgalitto,* alone or in combination with *Parikh* and *Caruso,* does not teach, suggest, or otherwise render obvious "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient," Applicants respectfully assert that claim 12 should be allowable at least for the same reasons stated above. Withdrawal of the rejection to claim 12 is respectfully requested.

Similarly, claim 21 should be allowable for the same reasons stated above as claim 21 depends on amended claim 18 and contain all the limitations of claim 18. Therefore, Applicants request withdrawal of the rejection and allowance of claim 21.

Claim Rejections under 35 U.S.C. § 112

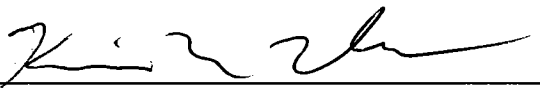
Claims 17, 22, 24, and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Particularly, the Examiner considers that the term "less than about" is a relative term that is not defined by the

claim and the specification provides no standard for ascertaining the requisite degree. Applicants respectfully disagree.

The subject specification does provide a standard for ascertaining the requisite degree that would allow one of ordinary skill in the art to determine an average size of the capsules. The Examiner is directed to the present specification, page 8, lines 24-27, which states an average diameter is measured as z average by quasielastic light scattering or photon correlation spectroscopy. Quasielastic light scattering (QLS) spectroscopy is a well-known optical method routinely used for particle size analysis for the determination of particle size, especially suitable in solution. Similarly, photon correlation spectroscopy (PCS) is routinely used in the art to investigate the dynamics of colloidal particles undergoing Brownian motion. This technique is applicable to, for example, low-density colloidal suspensions in which the effects of multiple light scattering are minimal. Therefore, it is believed that ordinary people skill in the art would reasonably appreciate the scope of the invention. "*When a term of degree is presented in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree. If it does not, a determination is made as to whether one of ordinary skill in the art, in view of the prior art and the status of the art, would be nevertheless reasonably apprised of the scope of the invention.*" *See* MPEP 2173.05(b). As a standard for determining average size of the capsules is disclosed in the specification, the limitation as claimed should have satisfied the requirement stated in MPEP. Withdrawal of the rejection to claims 17, 22, 24, and 26 is respectfully requested.

Having addressed all issues set out in the Office Action, Applicants respectfully submit that the claims are in condition for allowance or in better form for appeal, and respectfully requests that the claims be allowed.

Respectfully submitted,



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